

Investigation of the effectiveness of silver-containing drugs for the treatment of tuberculosis in the respiratory system

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ABSTRACT

Tuberculosis lesion of the upper respiratory tract in most cases is a secondary disease and develops as a result of the introduction of a specific pathogen in patients suffering from pulmonary tuberculosis. Against the background of the deterioration of the general epidemiological situation of tuberculosis, its course has changed in the direction of aggravation of the process and an increase in diseases of extrapulmonary tuberculosis. It is known that silver nanoparticles restore the sensitivity of drug-resistant strains of tuberculosis microbacteria to chemotherapy drugs, and their growth is suppressed. The purpose of the study is to evaluate the effectiveness of the use of silver-containing drugs for the treatment of patients with tuberculosis of the upper respiratory tract. As a result of the study, it was found that silver nanoparticles demonstrate anti-tuberculosis activity. At the same time, the dose-dependent nature of the suppressive activity of nanoparticles was established. Argitos at a concentration of 3.3% showed higher therapeutic activity in the treatment of laryngeal tuberculosis compared with standard anti-tuberculosis drugs.

Keywords: Tuberculosis, Extrapulmonary tuberculosis, Upper respiratory tract, Argitos, Protargol, Silver nanoparticles

Introduction

Tuberculosis lesion of the upper respiratory tract in most cases is a secondary disease and develops as a result of the introduction of a specific pathogen in patients suffering from pulmonary tuberculosis [1, 2]. Theoretically, primary localization of tuberculosis in one or another segment of the respiratory tract is also possible, but in clinical practice, this form is relatively rare [3]. The only exception is the nasal cavity, where, due to its

accessibility to external influences, it is possible to directly introduce Koch sticks from the outside and develop a tuberculous process [4]. The infection, as a rule, penetrates through the cracks of the entrance to the nose, where it enters from the air or is carried by the patient's finger [5]. Laryngeal and pharyngeal disease occurs due to the constant action of infected sputum expectorated by the patient on the mucous membrane [6]. The predisposing factor is the formation of small abrasions on the mucous membrane, where the continuity of the epithelial cover is disrupted. Such changes are very common in people suffering from chronic laryngitis, and this explains the more frequent development of laryngeal tuberculosis in men than in women [7]. Laryngeal tuberculosis is relatively rare in childhood. Diseases of the mucous membrane of the pharynx, tongue, and oral cavity are usually observed only in far-reaching cases of pulmonary tuberculosis when difficulty expectoration and a decrease in the overall resistance of the body contribute to sputum infection [8].

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Against the background of the deterioration of the general epidemiological situation of tuberculosis, its course has changed towards a heavier process, an increase in diseases of extrapulmonary tuberculosis and complications due to the development of drug resistance of mycobacterium tuberculosis to anti-tuberculosis drugs [9-12]. In this regard, the search for new pharmacological agents for the treatment of tuberculosis of the respiratory tract is relevant. Silver nanoparticles contained in preparations that are successfully used in clinical practice for various diseases, including diseases of the ENT organs, can become one of such means [13-16]. The results of several studies indicate the ability of silver nanoparticles to overcome the drug resistance of several pathogens, in particular Mycobacterium tuberculosis (MBT) [17-21]. It was found that silver nanoparticles restore the sensitivity of drug-resistant strains of tuberculosis micro bacteria to chemotherapy drugs, and their growth is suppressed [22].

Such medical preparations are Argitos and Protargol. Argitos is a preparation of colloidal silver. It is a means of protecting the nasal and laryngeal cavities in acute respiratory viral infections, herpes, and tonsillitis. It contains 10 mg/ml of silver [23].

Protargol is a silver-containing drug that has antiseptic, anti-inflammatory, and astringent effects [24, 25]. The drug Protargol is widely used in the treatment of inflammatory (especially purulent) processes in ophthalmology and otorhinolaryngology, urology. In comparison with antibiotics, taking the drug Protargol does not lead to dysbiosis. The preparation is an aqueous solution of silver proteinate in a concentration of 0.2 g / 10 ml.

The study aimed to evaluate the effectiveness and expediency of using nanosilver Argitos and Protargol preparations for the treatment of patients with tuberculosis of the upper respiratory tract, differing in the concentration of the latter.

Materials and Methods

The study was conducted at the Dagestan tuberculosis dispensary. The clinical use of a drug containing silver

nanoparticles in the treatment of drug-resistant tuberculosis of the upper respiratory tract was preceded by an experimental study to determine the antibacterial activity of Argitos and Protargol cluster silver preparations. For this purpose, 8 types of crops (experimental complexes) of mycobacterium cultures isolated from the sputum of patients with various forms of tuberculosis of the lungs and upper respiratory tract, with drug resistance to the minimum concentration of isoniazid (MBT 1), as well as to the minimum and maximum concentrations of isoniazid (MBT 2), were prepared on Levenstein—Jensen nutrient media, containing silver nanoparticles in different concentrations. The drug resistance of MBT to anti-tuberculosis drugs was determined by the method of absolute concentrations. The following gradations of growth suppression of the pathogen were distinguished: "complete" — no colony growth, "moderate" — 20-100 colonies, and "no growth suppression" — more than 100 colonies.

The clinical study included 100 patients with laryngeal tuberculosis aged 26 to 55 years. All patients had previously received voluntary informed consent to participate in the study. Patients of the main group (n=60) as part of the complex treatment of tuberculosis of the lungs and larynx were inhaled Argitos at a concentration of 3.3% for 10 minutes daily 2 times a day for 2 months. Patients of the control group (n=40) received standard anti-tuberculosis therapy.

Statistical processing of the results of the study was carried out using the Excel 2010 program with the determination of the arithmetic mean (M), the error of the arithmetic mean (m), and the confidence level (p). The confidence level was assessed as sufficient at $p < 0.05$.

Results and Discussion

Silver nanoparticles in an in vitro experiment demonstrated the dose-dependent nature of the suppressive activity against the drug resistance of Mycobacterium tuberculosis (**Table 1**).

Table 1. The suppressive activity of drugs containing silver nanoparticles on the growth of drug-resistant mycobacterium tuberculosis

Experimental complexes	The degree of suppression of the growth of drug resistance of MBT strains							
	Total		Full		Moderate		Absent	
	Absolute	%	Absolute	%	Absolute	%	Absolute	%
Protargol 1/5 + MBT 1	96	100			96	100		
Protargol 1/5 + MBT 2	100	100	-	-	28	25	72	72
Protargol 1/10 + MBT 1	96	100	-	-	50	52,1	46	49,7
Protargol 1/10 + MBT 2	100	100	-	-	-	-	100	100
Argitos 1,8% + MBT 1	96	100	96	100	-	-	-	-
Argitos 1,8% + MBT 2	100	100	48	48	52	52	-	-
Argitos 3,3% + MBT 1	96	100	96	100	-	-	-	-
Argitos 3,3% + MBT 2	100	100	100	100	-	-	-	-

The drug Protargol did not cause complete suppression of growth in any experiment. Moderate suppression of the growth of MBT with drug resistance to the minimum concentration of isoniazid was detected in 100% of cases when using the drug in a dilution of 1/5, whereas in a dilution of 1/10 moderate suppression of growth was detected in 52.1% of cases. There was a complete absence of bactericidal action in drug resistance to minimum and maximum concentrations of isoniazid.

Argitos solution in a concentration of 1.8% showed a bactericidal effect on *Mycobacterium tuberculosis*, which is drug resistant to a minimum concentration of isoniazid, in 100% of cases, with drug resistance to minimum and maximum concentrations of isoniazid — in 48%. 3.3% solution of Argitos drug had a 100% bactericidal effect against drug-resistant mycobacteria as a

minimum concentration isoniazid, and to the maximum, in connection with which it was used to conduct a clinical trial.

The effectiveness of the clinical use of Argitos was evaluated based on clinical, laboratory, radiological, and bacteriological data.

28 (56%) patients had impaired vocal function in the form of dysphonia of varying severity (from mild hoarseness to aphonia). A comparative analysis of the dynamics of restoration of vocal function in the two study groups indicates a higher therapeutic efficacy of the drug containing silver nanoparticles in the treatment of upper respiratory tract tuberculosis compared with standard anti-tuberculosis therapy. The dynamics of the restoration of voice function in the experimental (E) and control (C) groups are presented in **Table 2**.

Table 2. Dynamics of restoration of vocal function in patients with laryngeal tuberculosis treated with a drug containing silver nanoparticles (E – Experienced Group, C – Control Group)

Dynamics of voice function restoration	7 days		14 days		1 month		2 months	
	Group							
	E	C	E	C	E	C	E	C
Absolute	34	22	34	22	34	22	34	22
%	100	100	100	100	100	100	100	100
Significant (abs.)	20	43	26	6	30	10	32	14
Significant (%)	58.8	18.2	76.4	27.3	88.2	45.4	94.1	63.6
Insignificant (abs.)	8	6	4	10	4	8	2	6
Insignificant (%)	23.5	27.3	11.8	45.4	11.8	36.4	5.9	27.3
Absent (abs.)	6	12	4	6	-	4	-	2
Absent (%)	17.7	54.5	11.8	27.3	-	18.2	-	9.1

All patients treated with a drug containing silver nanoparticles showed positive dynamics at the 2nd month of treatment in the form of resorption of infiltrates and scarring of ulcers, while in the control group, 30% of patients had no positive dynamics of

the laryngoscopic picture, which indicates a higher therapeutic efficacy of the drug containing silver nanoparticles, according to compared with standard anti-tuberculosis therapy. The dynamics of the laryngoscopic pattern are presented in **Table 3**.

Table 3. Dynamics of the laryngoscopic picture in patients with laryngeal tuberculosis treated with a drug containing silver nanoparticles

Dynamics of the laryngoscopic picture	7 days		14 days		1 month		2 months	
	Group							
	E	C	E	C	E	C	E	C
Absolute	60	40	60	40	60	40	60	40
%	100	100	100	100	100	100	100	100
Infiltration resorption (abs.)	28	8	36	18	44	24	48	24
Infiltration resorption (%)	46.7	20	60	45	73.4	60	80	60
Scarring of the ulcer (abs.)	-	-	-	-	8	8	12	4
Scarring of the ulcer (%)	-	-	-	-	13.3	5	20	10
Absent (abs.)	32	32	24	22	8	14	-	12
Absent (%)	53.3	80	40	55	13.3	35	-	30

During 2 months of therapy, sputum stopped secreting in 32 (53.3%) patients of the experimental group, whereas in the control group – in 16 (40%) patients receiving treatment. MBT isolation stopped after 30 days in 73.3% of patients in the experimental group and 40% of the control group. After 2

months of therapy using a drug containing silver nanoparticles, sputum negation was observed in 93.3% of patients in the experimental group and 70% of patients receiving standard anti-tuberculosis therapy.

Conclusion

Silver nanoparticles in an in vitro experiment demonstrated anti-tuberculosis activity against resistant strains of the pathogen. In an in vitro experiment, the dose-dependent nature of the suppressive activity of nanoparticles was established, while Argitos showed maximum activity at a concentration of 3.3%. Argitos at a concentration of 3.3% showed higher therapeutic activity in the treatment of laryngeal tuberculosis compared with standard anti-tuberculosis drugs, which was characterized by a faster restoration of vocal function, resorption of infiltrates in the larynx, scarring of its ulcerative lesions, a decrease in the timing of bacterial excretion and the amount of sputum secreted. For local treatment of tuberculosis of the upper respiratory tract, inhalation administration of Argitos at a concentration of 3.3% daily 2 times a day for 10 minutes for 2 months is recommended.

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